Antidepressant drug use in glioblastoma patients: an epidemiological view.

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Abstract: Background: Antidepressant drugs have shown antitumor activity in preclinical glioblastoma studies. Antidepressant drug use, as well as its association with survival, in glioblastoma patients has not been well characterized on a population level. Methods: Patient characteristics, including the frequency of antidepressant drug use, were assessed in a glioblastoma cohort diagnosed in a 10-year time frame between 2005 and 2014 in the Canton of Zurich, Switzerland. Cox proportional hazards regression models were applied for multivariate analysis. Kaplan-Meier survival curves were used to estimate overall survival (OS) data and the log-rank test was performed for comparisons. Results: A total of 404 patients with isocitrate dehydrogenase wild-type glioblastoma were included in this study. Sixty-five patients (16.1%) took antidepressant drugs at some point during the disease course. Patients were most commonly prescribed selective serotonin reuptake inhibitors at any time (N = 46, 70.8%). Nineteen patients (29.2%) were on antidepressant drugs at the time of their tumor diagnosis. No differences were observed in OS between those patients who had taken antidepressants at some point in their disease course and those who had not (P = .356). These data were confirmed in a multivariate analysis including age, Karnofsky Performance Scale (KPS), sex, extent of resection, O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation status, and first-line treatment as cofounders (P = .315). Also, there was no association of use of drugs modulating voltage-dependent potassium channels (citalopram; escitalopram) with survival (P = .639). Conclusions: This signal-seeking study does not support the hypothesis that antidepressants have antitumor efficacy in glioblastoma on a population level.

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Antidepressant drug use in glioblastoma patients: an epidemiological view

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Conflict of interest

MW has received research grants from Abbvie, Adastra, Bristol Meyer Squibb (BMS), Dracen, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, Piqur and Roche, and honoraria for lectures or advisory board participation or consulting from Abbvie, Basilea, Bristol Meyer Squibb (BMS), Celgene, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, Orbus, Roche and Tocagen.

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Abstract

Purpose: Antidepressant drugs have shown anti-tumor activity in preclinical glioblastoma studies. Antidepressant drug use, as well as its association with survival, in glioblastoma patients has not been well characterized on a population level.

Methods: Patient characteristics, including the frequency of antidepressant drug use, were assessed in a glioblastoma cohort diagnosed in a 10-year time-frame between 2005 and 2014 in the Canton of Zurich, Switzerland. Cox proportional hazards regression models were applied for multivariate analysis. Kaplan-Meier survival curves were used to estimate overall survival data and the log-rank test was performed for comparisons.

Results: Four hundred four patients with isocitrate dehydrogenase (IDH) wildtype glioblastoma were included in this study. Sixty-five patients (16.1%) took antidepressant drugs at some point during the disease course. Patients were most commonly prescribed selective serotonin reuptake inhibitors at any time (N=46, 70.8%). Nineteen patients (29.2%) were on antidepressant drugs at the time of their tumor diagnosis. No differences were observed in overall survival between those patients who had taken antidepressants at some point in their disease course and those who had not (p=0.356). These data were confirmed in a multivariate analysis including age, Karnofsky performance status, gender, extent of resection, O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation status, and first-line treatment as cofounders (p=0.315). Also, there was no association of use of drugs modulating voltage-dependent potassium channels (citalopram; escitalopram) with survival (p=0.639).

Conclusions: This signal-seeking study does not support the hypothesis that antidepressants have antitumor efficacy in glioblastoma on a population level.

Keywords: antidepressants; depression; epidemiology; glioblastoma; survival.

Introduction

Glioblastoma is the most common malignant primary brain tumor in adults [1] Despite multi-modal care regimens, including maximum safe tumor resection, radiotherapy and chemotherapy [2,3], prognosis remains poor with a median survival of 11 to 14 months [4,5] and a five-year survival rate of 5.6% on a population-based level [1]. Glioblastoma causes cognitive deficits and psychiatric comorbidity, such as depression, anxiety, or fatigue [6-8]. The prevalence of depression among brain tumor patients has been reported in a wide range of less than 1% [9] to up to 90% [10] of patients and is likely highly dependent on the methodology used to assess depressive symptoms. Patient-rated analyses showed higher prevalence of depression (27%) than clinician-rated measures (15%), as discussed in a systematic review of observational studies on depression in glioma [11]. This study found a prevalence of depression in about 15% of glioma patients. The presence of depressive symptoms may be independently associated with shorter overall survival (OS) in glioblastoma patients [12]. In preclinical models, tricyclic antidepressants (TCA) such as imipramine or amitriptyline, acting as mixed norepinephrine and serotonin uptake inhibitors can impair the malignant phenotype of glioma cells by inhibiting cellular respiration, an indicator of apoptosis [13,14]. Moreover, imipramine and amitriptyline inhibit the expression of p65 NF-κB, frequently overexpressed in glioblastoma cells, which results in reduced tumor cell proliferation, motility and survival [15,16]. *In vitro* data suggest a role for voltage-dependent potassium channels as therapeutic targets in gliomas, which can be modulated by different classes of antidepressants [17,18]. The Kv10.1 subtype of potassium channels is highly expressed in gliomas [19]. Imipramine, a TCA, binds to these Kv10.1 channels and decreases the proliferation rate of cancer cells [20]. Glioma cells exhibit a high mitochondrial membrane potential and low expression of Kv1.5 channels. Citalopram, a selective serotonin reuptake inhibitor (SSRI), acts on the Kv1.5 subtype as an open-channel blocker and increases the intracellular potassium concentration, leads to

decreased resistance to apoptosis [21,22]. Escitalopram, a stereoisomer of citalopram, also inhibits voltage-dependent potassium channels, but data regarding its activity against glioma cells are lacking [23]. Imipramine also inhibits the PI3K/Akt/mTOR signaling pathway and induces autophagic cell death in U87MG glioma cells [24]. Finally, there is evidence from a mouse model suggesting that fluoxetine, a SSRI, can suppress the growth of experimental gliomas by directly binding to the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) [25]. On a population-based level, the prevalence of antidepressant drug use among glioblastoma patients, as a surrogate marker for depression or depressive symptoms, as well as the association of use of such agents with survival remains unclear.

Methods

Patient identification

All patients 18 years or older who were inhabitants of the Canton of Zürich, Switzerland and diagnosed with glioblastoma between 2005 and 2014 were included in a glioblastoma cancer registry in the Canton of Zurich, Switzerland. Patient identification data were provided by the Cancer Registry of the Cantons Zurich and Zug. Epidemiological data on this patient cohort have been published previously [4,5]. For the present analysis, we excluded all patients who lacked molecular data on the IDH mutation status based on the present World Health Organization (WHO) classification [26], or who had insufficient patient documentation on antidepressant drug use (see Supplementary Figure 1).

Disease characteristics

All tumors in the glioblastoma cancer registry had been classified according to the WHO 2007 criteria [27] in the local pathology departments, and in a second step were classified by IDH mutation status in accordance with the WHO 2016 classification [26]. The O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation status was determined by methylation-specific PCR. IDH mutation status was obtained by immunohistochemistry for IDH1 R132H, mainly, based on the suggestion that sequencing may not be needed in patients older than 55 years of age [26]. Extent of resection was determined by early postoperative magnetic resonance imaging (MRI) or, if no MRI was available, by cranial computed tomography (CT). Macroscopic (gross) total resection was defined by the absence of contrast enhancement [28]. Data on use of antidepressant drugs were extracted from clinical records. For most patients we had access to all appropriate medical records, provided by the caregivers of the patients who we contacted directly. For patients seen at the University Hospital in Zurich the drug use in general was documented almost every

time the patient had an appointment. Nevertheless, we cannot exclude that there are patients who received antidepressants that we were not aware of.

Statistical analyses

Demographical, clinical, molecular marker and use of antidepressant drug data were obtained to apply descriptive statistics. The Chi-square test was performed for analysis of nominal variables, and the Mann-Whitney U test was used for the comparison of quantitative variables between the two patient cohorts of antidepressant drug users and non-users. OS was calculated from primary surgery to death or last follow-up. Patients were censored at last follow-up. Kaplan-Meier curves were used to estimate OS in the antidepressant drug users and non-users, differences were analyzed using the log-rank test. Cox proportional hazards regression models were used for multivariate analysis to test the association of clinical and molecular factors, as well as use of antidepressant drugs with outcome. The multivariate model was applied to all patients who had complete information on all tested co-variables. All statistical analyses were performed using IBM SPSS, Version 24 (IBM Corporation, Armonk, NY) statistical software, and a p value of 0.05 was set as statistically significant.

Ethics

This study was approved by the Ethics Committee of the Canton of Zurich (KEK-ZH-Nr. 2009-0135/1; KEK-ZH-Nr. 2015-0437).

Results

Patient characteristics

Four hundred four patients with IDH wildtype glioblastoma were included in this retrospective study; 65 of these 404 patients (16.1%) took antidepressant drugs at some point during their disease course. Patient characteristics of the two subpopulations, the non-antidepressant cohort (N=339) and antidepressant cohort (N=65), are summarized in Table 1. Age, gender, KPS, extent of resection and first-line treatment after initial surgery were balanced between both patient cohorts. Patients who received antidepressants more frequently had a methylated MGMT promoter methylation status than patients who did not (p=0.014). The distribution of the KPS differed between both patient groups (p=0.033). Comparing the use of antidepressant drugs over the analyzed 10-year time-frame, the frequency of use of antidepressant drugs among glioblastoma patients decreased over the years from 22.6% (N=40 patients out of N=177 patients) in the years 2005 through 2009 to 10.4% (N=25 patients out of N=241 patients) in the years 2010 through 2014 (p=0.001) (Table 1).

Patterns of antidepressant drug use

Patients who had taken antidepressant drugs at the time of their glioblastoma diagnosis most often received SSRI (68.4%), followed by tetracyclic antidepressants (TeCA) (26.8%), and selective serotonin-norepinephrine reuptake inhibitors (SSNRI) (5.3%). After 3 and 6 months since beginning to take antidepressants, about half of the patients continued treatment (57.9% and 47.4%, respectively). When focusing on antidepressants at any time during the course of the disease, SSRI were still the most frequently used drugs (70.8%), especially citalopram (33.8%); 15.4% of all patients received more than only one antidepressant agent (Table 2). Additionally, of the 65 antidepressant drug-using patients, 41 (63.1%) were on co-medication with

benzodiazepines at some point during their disease trajectory (see Supplementary Table 1).

Outcome data

Median OS was 12.8 months (95% confidence interval (CI) 11.4-14.1 months) for patients without antidepressant drug use and 10.8 months (95% CI 7.9-13.6 months) for patients who had antidepressants at any time during the course of the disease (Table 3). None of the patients included in this study were reported to have committed suicide. OS data, estimated using Kaplan-Meier curves, for both the antidepressant drug using and non-using subgroups are displayed in Figure 1A. Although there was a trend towards worse survival in patients with antidepressant drug use when compared to non-users, no statistically significant differences were observed (p=0.356) (Table 3, Fig. 1A).

The two patient cohorts, antidepressant - and no antidepressant drug-users, were not balanced regarding the MGMT promoter methylation status (Table 1). Therefore, survival curves were analyzed separately for patients with tumors with a methylated or unmethylated MGMT promoter. A trend towards inferior survival was noticed in both patient cohorts, especially in the patients with a methylated MGMT promoter methylation status, but for both patient subgroups this did not reach statistically significance (methylated MGMT promoter status p=0.423, unmethylated MGMT promoter status p=0.787) (Table 3, see Supplementary Figure 2).

When analyzing the two 5-year time-frames separately, no association with OS was seen either (see Supplementary Table 2). In a subgroup analysis focused on those patients who had used antidepressant drugs previously reported to modulate voltage-dependent potassium channels in glioma cells [17], such as citalopram (N=22) or escitalopram (N=16) (median OS 10.4 months, 95% CI 7.4-13.4), no association with OS was seen compared to patients with any other antidepressant drug use (median OS 11.9 months, 95% CI 6.0-17.9; p=0.920) or no antidepressant medication

(median OS 12.8 months, 95% CI 11.4-14.1; p=0.551) (Fig. 1B).

Multivariate analysis with regards to death

Multivariate analysis was performed to assess the association of clinical and molecular parameters with OS. The analysis confirmed known prognostic or predictive markers in glioblastoma, including age, KPS, extent of resection, MGMT promoter methylation status, or first-line treatment. Antidepressant drug use at any time during the course of the disease was not associated with survival (HR 0.83, 95% CI 0.58-1.19) (Table 4).

Discussion

Antidepressant drugs may be given to glioblastoma patients for different reasons, including depression, fatigue, anxiety, or inappetence. These symptoms may be caused by the tumor itself, tumor-specific treatments, side-effects of medications, or a psychiatric disorder in the medical history [8,11,29]. In our cohort study in the Canton of Zurich, Switzerland, 65 patients (16.1%) diagnosed with IDH wildtype glioblastoma were on antidepressant drugs at some time during the course of disease (Table 1). Assuming that most patients received these drugs because of psychiatric morbidities, mainly depressive symptoms and that therefore antidepressant drug use can be used as a surrogate marker for depression, the frequency of depression in this cohort is in line with data of observational studies published in 2010 [11], although higher prevalence rates have also been reported [10]. This may underline differences in the awareness of psychiatric disorders in glioblastoma patients, which can be influenced by social, cultural, and other regional factors. Interestingly, use of antidepressant drugs among glioblastoma patients decreased over the years in Zurich, Switzerland (see Supplementary Table 2). Not all glioblastoma patients diagnosed with psychiatric symptoms receive drugs, and non-medication approaches to psychiatric comorbidity may be more compatible with social life. Importantly, there may be an increased awareness for such non-pharmaceutical approaches to treating psychiatric symptoms and comorbidities in the general population. This is also shown by increased use of complementary and alternative medicine (CAM) in glioma patients [30,31].

Putative molecular mechanisms of anticancer activity of antidepressant drugs include modulations of the PI3K/Akt/mTOR signaling pathway [24], AMPAR-mediated calcium-dependent apoptosis [25], influencing the mitochondrial machinery [14,21], or targeting voltage-dependent potassium channels [17,18]. In our population-based study no association was found between the use of antidepressant drugs and survival (Fig. 1A, Table 3). Moreover, although not statistically

significant, median OS was numerically inferior in the antidepressant cohort compared to patients who had no antidepressant drugs, independent of the MGMT promoter methylation status (Table 3, see Supplementary Figure 2). The same was true when we analyzed the subgroup of patients who had taken antidepressant drugs which interfered with voltage-dependent potassium channels, including citalopram and escitalopram (both SSRI) (Fig. 1B). In line with our data, in a retrospective study, performed at the Mayo Clinic in Rochester, Minnesota, no association of SSRI use with survival in glioblastoma patients was found [32]. In contrast to our data in glioblastoma patients, the opposite was seen in non-central nervous system cancers, such as breast cancer [33,34].

Limitations of our study include the retrospective nature of the study, as well as the lack of data on the diagnosis of psychiatric disorders, and intensity of treatment with antidepressants. However, medications, including antidepressant drugs, were documented routinely in most patients. Based on the retrospective nature of data collection, the prevalence of drug prescription may be underestimated.

The administration of antidepressant drugs at the time of diagnosis or during the course of the disease was not associated with survival in our glioblastoma cohort. This study does not support the hypothesis that antidepressant drugs may have antitumor efficacy on a population-based level, not excluding the possibility of a subpopulation effect not addressed by our study design. However, further investigation, mainly in prospective studies and with a standardized psychiatric assessment, may be necessary to dissect any associations of psychiatric comorbidity and the associated therapeutic interventions with outcome.

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Figure captions

Figure 1. Antidepressant drugs and survival.

(A) Kaplan-Meier curves of overall survival are shown for patients who had antidepressant drugs (black) or who had no antidepressant drugs (grey) at any time during the course of the disease.

(B) The same Kaplan-Meier survival curves are shown now stratified for patients who had drugs modulating voltage-dependent potassium channels (blue; citalopram, escitalopram) and those who had any other antidepressant drugs (green). The log rank test was used for comparison.

Table 1. Patient characteristics, IDH wildtype cohort.

	Non-antidepressant drug cohort N=339	**Antidepressant drug cohort N=65**	**P value**
Age, years			
Median	62.8	61.3	0.878
Range	18-90	31-86	
Gender, N (%)			
Male	216 (63.7)	40 (61.5)	0.738
Female	123 (36.2)	25 (38.5)	
KPS*, N (%)			
90-100%	54 (16.1)	5 (7.7)	0.033
70-80%	191 (56.8)	48 (73.8)	
< 70%	91 (27.1)	12 (18.5)	
No data	3	-	
Extent of surgical resection*, N (%)	56 (16.6)	6 (9.2)	0.395
Gross total resection	202 (59.8)	45 (69.2)	
Incomplete resection	79 (23.4)	14 (21.5)	
Biopsy	1 (0.3)	-	
Autopsy	1	-	
No data			
First-line therapy, N (%)			
RT plus TMZ	170 (50.1)	33 (50.8)	0.538
RT alone	65 (19.2)	11 (16.9)	
CT alone	25 (7.4)	2 (3.1)	

Others[§]	23 (6.8)	4 (6.2)	
No therapy	51 (15.0)	14 (21.5)	
No data	5	1	
MGMT promoter methylation status, N (% per number of patients with assessed data)			
Methylated	97 (40.9)	30 (60.0)	0.014
Unmethylated	140 (59.1)	20 (40.0)	
No data	102	15	
Analyzed time-frame			
2005-2009	129 (38.1)	40 (61.5)	<0.001
2010-2014	210 (61.9)	25 (38.4)	

N, number of patients; IDH, isocitrate dehydrogenase; KPS, Karnofsky performance score; MGMT, O^6-methylguanine DNA methyltransferase; RT, radiotherapy; TMZ, temozolomide; CT, chemotherapy (mostly alkylating chemotherapy); *, at time of diagnosis; [§], mainly experimental drugs in clinical trials, or bevacizumab.

Table 2. Antidepressant drug use in glioblastoma patients, stratified by mode of action and timepoint.

	Antidepressant drug cohort
Antidepressants at time of diagnosis, N	**19**
Type of antidepressant drug, N (% of those with antidepressant drug use at diagnosis)[+]	
TeCA (mirtazapine)	7 (36.8)
SSRI	13 (68.4)
Citalopram	6 (31.6)
Escitalopram	5 (26.3)
Fluoxetine	1 (5.3)
Sertraline	1 (5.3)
SSNRI (venlafaxine)	1 (5.3)
Antidepressants 3 months after diagnosis, N (% of those with antidepressant drug use at diagnosis)	
Ongoing	11 (57.9)
Not ongoing	2 (10.5)
Switched antidepressants	3 (15.8)
No data	3 (15.8)
Antidepressants 6 months after diagnosis, N (% of those with antidepressant drug use at diagnosis)	
Ongoing	9 (47.4)
Not ongoing	1 (5.3)

Switched antidepressants	3 (15.8)
No data	6 (31.6)
Antidepressants at any time, N	**65**
Type of antidepressant drug, N (% of those with any antidepressant drug use) [+]	
TCA (amitriptyline)	1 (1.5)
TeCA (mirtazapine)	23 (35.4)
SSRI	46 (70.8)
Citalopram	22 (33.8)
Escitalopram	16 (24.6)
Fluoxetine	1 (1.5)
Sertraline	7 (10.8)
SSNRI (venlafaxine)	5 (7.7)
Multiple antidepressants[++]	10 (15.4)
SSRI and TeCA	7 (10.8)
SSRI and SSNRI	1 (1.5)
Multiple SSRIs	1 (1.5)
TeCA and SSNRI	1 (1.5)

N, number of patients; TCA, tricyclic antidepressant; TeCA, tetracyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SSNRI, selective serotonin-norepinephrine reuptake inhibitor; [+], patients could have taken more than one antidepressant drug at the same time [++], each antidepressant in this category has been counted in its individual group as well.

Table 3. Overall survival data, IDH wildtype cohort.

	N (events)	Median OS in months (95% CI)	OS 12-months in % (SE; remaining cases)	OS 24-months in % (SE; remaining cases)	P value
All patients					
No antidepressants	339 (281)	12.8 (11.4-14.1)	54.4 (2.8; 160)	19.0 (2.3; 52)	0.356
Antidepressants	65 (51)	10.8 (7.9-13.6)	44.3 (6.7; 23)	17.5 (5.4; 8)	
All patients					
Methylated MGMT promoter	127 (101)	14.2 (9.3-19.0)	61.5 (4.5; 68)	31.3 (4.5; 32)	0.004
Unmethylated MGMT Promoter	160 (136)	12.2 (10.8-13.6)	51.7 (4.2; 71)	14.0 (3.0; 18)	
Patients with a methylated MGMT promoter					
No antidepressants	97 (78)	14.4 (8.7-20.0)	61.2 (5.1; 53)	33.2 (5.1; 26)	0.423
Antidepressants	30 (23)	13.4 (11.4-15.3)	62.4 (9.4; 16)	25.0 (8.7; 6)	

Patients with an unmethylated MGMT promoter					
No antidepressants	140 (121)	12.3 (10.7-13.8)	52.4 (4.4; 64)	12.8 (3.1; 15)	0.787
Antidepressants	20 (15)	11.9 (6.7-17.1)	45.2 (12.5; 7)	23.2 (11.2; 3)	

N, number of patients; OS, overall survival; CI, confidence interval; SE, standard error; MGMT, O^6-methylguanine DNA methyltransferase.

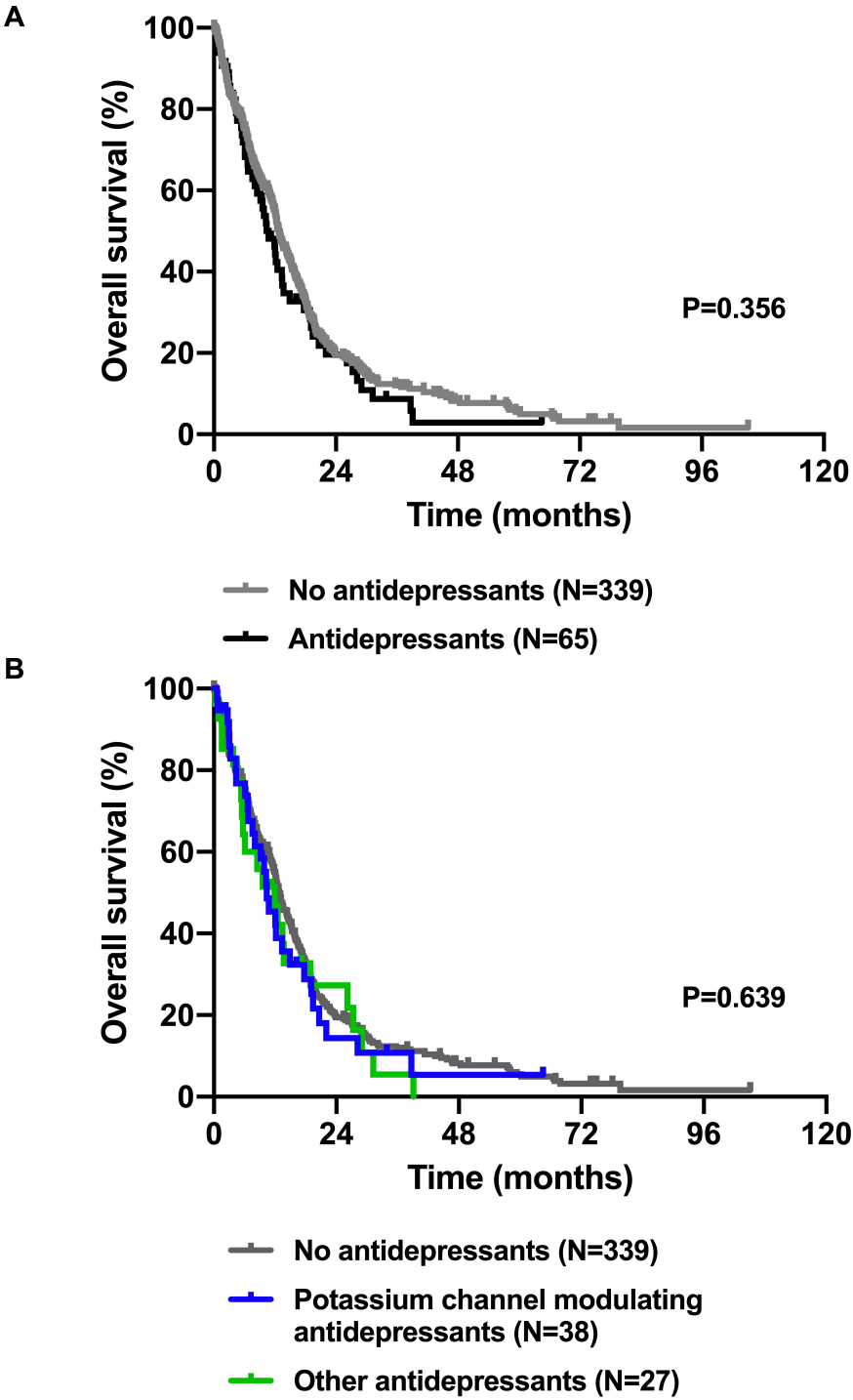
Table 4. Multivariate analysis with regards to death (cox regression).

	N	HR (95% CI)	P value
Age			
> 65 years	120	1	ref
≤ 65 years	162	0.70 (0.51-0.97)	0.030
KPS*			
< 70%	67	2.22 (1.58-3.11)	<0.001
70-80%	171	1	ref
90-100%	44	0.68 (0.46-1.01)	0.054
Gender			
Male	185	1	ref
Female	97	1.16 (0.88-1.54)	0.302
Extent of resection			
Biopsy	50	1	ref
Incomplete	194	0.38 (0.26-0.56)	<0.001
Gross total (≥ 99%)	38	0.22 (0.13-0.36)	<0.001
MGMT promoter methylation status			
Unmethylated	159	1	ref
Methylated	123	0.31 (0.17-0.55)	<0.001
Postsurgical therapy			
No therapy	34	2.67 (1.6-4.48)	<0.001
RT alone	51	1	ref
CT alone	23	0.95 (0.54-1.67)	0.848

RT plus TMZ	156	0.44 (0.29-0.67)	<0.001
Others[§]	18	0.40 (0.21-0.77)	0.006
Antidepressant drug			
No	233	0.83 (0.58-1.19)	0.315
Yes	49	1	ref

RT, radiotherapy; CT, chemotherapy; TMZ, temozolomide; CI, confidence interval; HR, hazard ratio; *, at time of diagnosis; [§], mainly experimental drugs in clinical trials, or bevacizumab.

Figure 1


A
100
80
60
40
20
0
Overall survival (%)
P=0.356
0
24
48
72
96
120
Time (months)
No antidepressants (N=339)
Antidepressants (N=65)
B
100
80
60
40
20
0
Overall survival (%)
P=0.639
0
24
48
72
96
120
Time (months)
No antidepressants (N=339)
Potassium channel modulating antidepressants (N=38)
Other antidepressants (N=27)

Supplementary Data

Antidepressant drug use in glioblastoma patients: an epidemiological view

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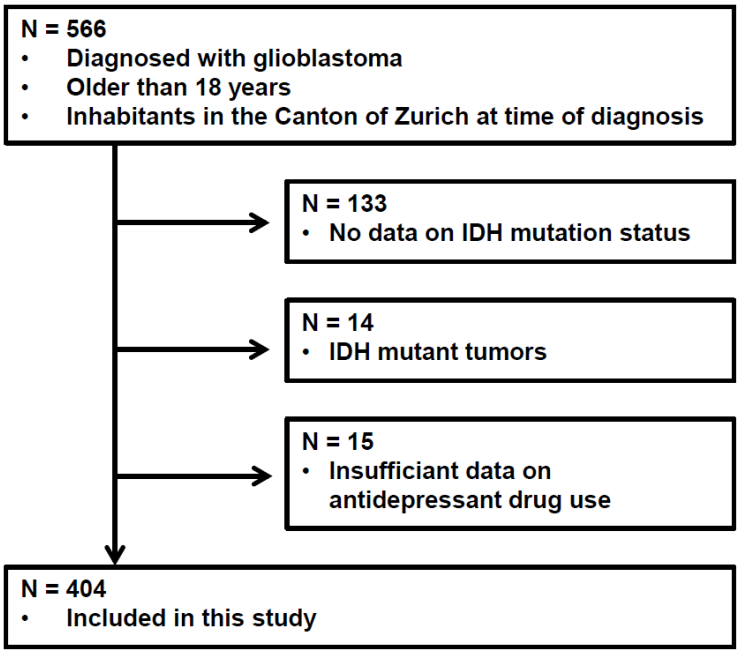
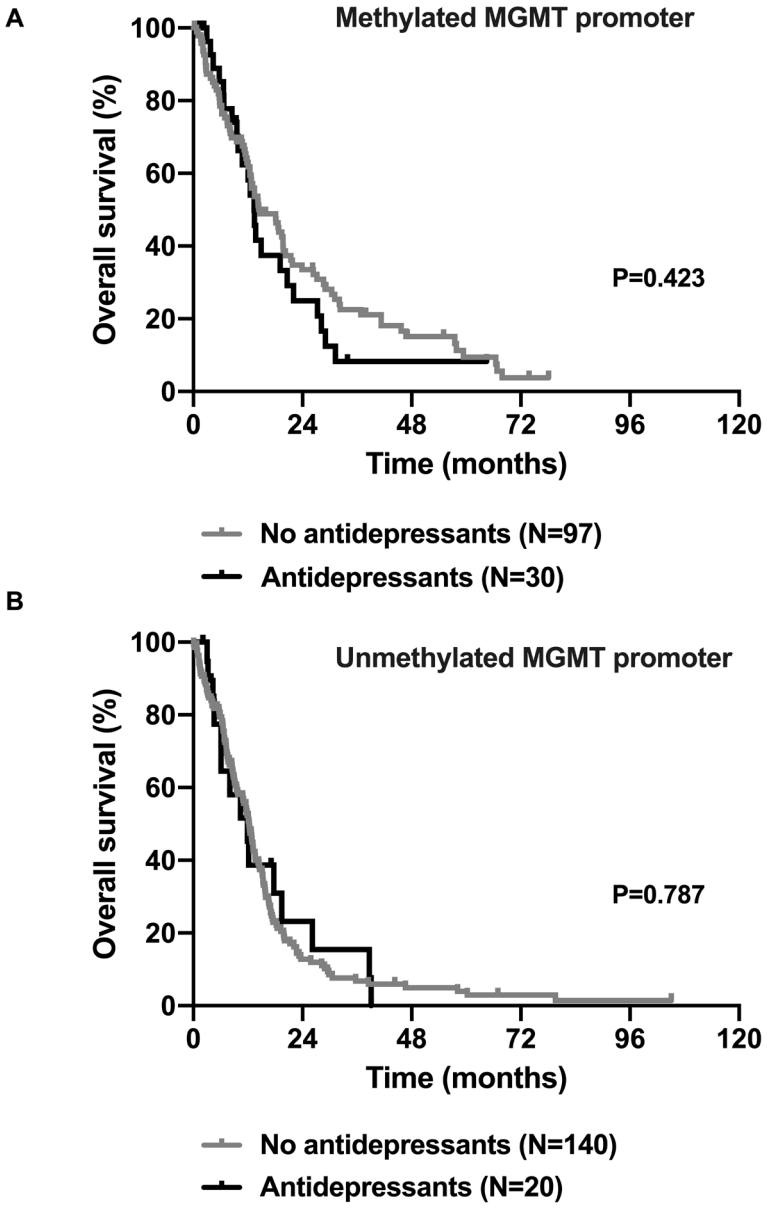
Supplementary Figure 1. Consort sheet.



Supplementary Figure 2. Antidepressant drugs and survival, stratified by MGMT promoter methylation status.

Kaplan-Meier curves of overall survival are shown for patients who had antidepressant drugs (black) or who had no antidepressant drugs (grey) at any time during the course of the disease. Data are shown for patients diagnosed with glioblastoma with (A) a methylated MGMT promoter, or (B) an unmethylated MGMT promoter. The log rank test was used for comparison.



Supplementary Table 1. Co-medication of benzodiazepines in glioblastoma patients with antidepressant drug use at any time during the course of the disease.

	Antidepressant cohort N = 65
Benzodiazepine use, N (%)	41 (63.1)
Type of benzodiazepine, N (% of those with any benzodiazepine use)	
Alprazolam	2 (4.9)
Clobazam	23 (56.1)
Diazepam	2 (4.9)
Lorazepam	22 (53.7)
Oxazepam	3 (7.3)
Multiple benzodiazepines [+]	11 (26.8)

N, number of patients; [+], each benzodiazepine in this category has been counted in its individual group as well.

Supplementary Table 2. Overall survival data, IDH wildtype cohort, stratified for the two 5-year time-frames.

	N (events)	**Median OS in months (95% CI)**	**OS 12-months in % (SE; remaining cases)**	**OS 24-months in % (SE; remaining cases)**	**P value**
2010-2014					
No antidepressants	210 (170)	14.2 (12.4-16.0)	60.1 (3.5; 108)	17.0 (2.9; 28)	0.461
Antidepressants	25 (20)	6.6 (3.5-9.7)	35.9 (10.0; 8)	23.9 (9.6; 4)	
2005-2009					
No antidepressants	129 (111)	11.0 (8.2-13.8)	44.4 (4.6; 51)	21.0 (3.8; 23)	0.804
Antidepressants	40 (31)	11.9 (9.6-14.2)	46.5 (8.7; 14)	10.0 (5.4; 3)	

N, number of patients; OS, overall survival; CI, confidence interval; SE, standard error.